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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/901,186	07/09/2001	George Perry	5877248933	6017

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EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 08/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/901,186	PERRY ET AL.	
	Examiner	Art Unit	
	Christopher J Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *7-9 and 13-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 10-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-17* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 July 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. The Response and Amendment filed 13 January 2004 has been received and entered in full.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

3. The Objection to the Specification as set forth at pp. 3 ¶6-7 in the previous Office Action (17 January 2003) is hereby *withdrawn* in view of Applicant's amendments (13 January 2004).

4. The Objection to the claims as set forth at pp. 3 ¶8 in the previous Office Action (17 January 2003) is *moot* in view of Applicant's amendments (13 January 2004).

5. The Rejection of claims **1-6** and **10-12** under 35 U.S.C. §112 ¶2 as set forth at pp. 3-4 ¶9 in the previous Office Action (17 January 2003) is *withdrawn* in view of Applicant's amendments (13 January 2004).

6. The Rejection of claims **1-6** and **10-12** under 35 U.S.C. §102(b) as set forth at pp. 4-5 ¶10-12 in the previous Office Action (17 January 2003) is *withdrawn* in view of Applicant's amendments (13 January 2004).

7. All Rejections and Objections not herein maintained or set forth are hereby *withdrawn.*

Drawings

8. The drawings are objected to because Figures 1-5 each have two parts, "AD" and "Control". These labels should be included in the Specification. Corrected drawing sheets are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the

remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. The replacement sheet(s) should be labeled "Replacement Sheet" in the page header (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims **1, 2, 4, 5,** and **6** are rejected under 35 U.S.C. 102(b) as being anticipated by Schipper *et al.* (June 1995) "Expression of Heme Oxygenase-1 in the Senescent and Alzheimer-diseased Brain." Ann Neurol **37**(6): 758-768. Schipper *et al.* teaches a method of measuring oxidative stress in Alzheimer's disease and age-matched control human patients via assessing the levels of Heme-oxygenase-1 (Abstract).

10. Schipper *et al.* teaches measuring Heme-oxygenase-1 (HO-1) in Alzheimer's disease and age-matched control human patients thus meeting the limitations of claims 1, 4, 5, and 6 (pp. 758-759).

11. Schipper *et al.* teaches measuring HO-1 in said patients samples from the hippocampus, cerebral cortex, and subcortical white matter thus meeting the limitations of claims 1, 2, and 3 (Figures 1-5; pp. 765).

12. Claims **1, 2, 4, 5,** and **6** are rejected under 35 U.S.C. 102(b) as being anticipated by Smith *et al.* (1998) "Cytochemical Demonstration of Oxidative Damage in Alzheimer Disease by Immunochemical Enhancement of the Carbonyl Reaction with 2,4-Dinitrophenylhydrazine." The Journal of Histochemistry & Cytochemistry **46**(6): 731-735. Smith *et al.* teaches a method of measuring oxidative stress in Alzheimer's disease and age-matched control human patients via detecting 2,4-Dinitrophenylhydrazine (HNE) (Abstract).

13. Smith *et al.* teaches measuring 2,4-Dinitrophenylhydrazine (HNE) in Alzheimer's disease and age-matched control human patients thus meeting the limitations of claims 1, 4, 5, and 6 (pp. 732; Figure 1).

14. Smith *et al.* teaches measuring HNE in said patients samples from the hippocampus thus meeting the limitations of claims 1, 2, and 3 (Figures 1-2; pp. 732, 734).

15. Claims **1, 2, 4, 5,** and **6** are rejected under 35 U.S.C. 102(b) as being anticipated by Smith *et al.* (7 June 1994) "Advanced Maillard reaction end products are associated with Alzheimer disease pathology." PNAS **91**(12): 5710-5714 (**IDS#CI**). Smith *et al.* teaches a method of measuring oxidative stress in Alzheimer's disease and age-matched control human patients via detecting pyrraline and pentosidine (Abstract).

16. Smith *et al.* teaches measuring pyrraline and pentosidine in Alzheimer's disease and age-matched control human patients thus meeting the limitations of claims 1, 4, 5, and 6 (pp. 5710; Figures 1 & 2).

17. Smith *et al.* teaches measuring pyrraline and pentosidine in said patients samples from the hippocampus thus meeting the limitations of claims 1, 2, and 3 (Figure 3; pp. 5711).

18. Claims **1, 2, 4,** and **5** are rejected under 35 U.S.C. 102(b) as being anticipated by Smith *et al.* (15 April 1997) "Widespread Peroxynitrite-Mediated Damage in Alzheimer's Disease." The Journal of Neuroscience **17**(8): 2653-2657. Smith *et al.* teaches a method of measuring oxidative stress in Alzheimer's disease and age-matched control human patients via detecting nitrotyrosine (NT) (Abstract).

19. Smith *et al.* teaches measuring nitrotyrosine (NT) in Alzheimer's disease and age-matched control human patients thus meeting the limitations of claims 1, 4, and 5 (pp. 2653).

20. Smith *et al.* teaches measuring NT in said patients samples from the hippocampus thus meeting the limitations of claims 1, 2, and 3 (Figures 1-2; pp. 2653, 2656).

21. Claims **1, 2, 4,** and **5** are rejected under 35 U.S.C. 102(b) as being anticipated by Nunomura *et al.* (15 March 1999) "RNA Oxidation Is A Prominent Feature of Vulnerable Neurons in Alzheimer's Disease." The Journal of Neuroscience **19**(6): 1959-1964 (**IDS#CC**). Nunomura *et al.* teaches a method of measuring oxidative stress in Alzheimer's disease and age-matched control human patients via detecting 8-hydroxyguanosine (8OHG) (Abstract).

22. Nunomura *et al.* teaches measuring 8-hydroxyguanosine (8OHG) in Alzheimer's disease and age-matched control human patients thus meeting the limitations of claims 1, 4, and 5 (pp. 1959-1961; Figure 2).

23. Nunomura *et al.* teaches measuring 8OHG in said patients samples from the hippocampus, subiculum, as well as the entrohinal, frontal, temporal, and occiptal neocortex thus meeting the limitations of claims 1, 2, and 3 (Figure 1; pp. 1959-1961).

24. Claims **1, 2, 4, 5,** and **6** are rejected under 35 U.S.C. 102(b) as being anticipated by Horie *et al.* (18 July 1997) "Immunohistochemical Localization of Advanced Glycation End Products, Pentosidine, and Carboxymethyllysine in Lipofusin Pigments of Alzheimer's Disease and Aged Neurons." Biochemical and Biophysical Research Communications **236**(2): 327-332. Horie *et al.*

teaches a method of measuring oxidative stress in Alzheimer's disease and age-matched control human patients via detecting pentosidine and carboxymethyllysine (Abstract).

25. Horie *et al.* teaches measuring pentosidine and carboxymethyllysine (CML) in Alzheimer's disease and age-matched control human patients thus meeting the limitations of claims 1, 4, 5, and 6 (pp. 336-337).

26. Horie *et al.* teaches measuring pentosidine and CML in said patients samples from the hippocampus thus meeting the limitations of claims 1, 2, and 3 (Figures 1-3).

27. Claims **1, 2, 4, 5,** and **6** are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent Application Publication 2003/0211622 A1 (13 November 2003) Roberts, II. US 2003/0211622 teaches a method of measuring oxidative stress in humans as a means of diagnosing Alzheimer's disease (claims 1 & 13; **[0008], [0103], [0138]**).

28. US 2003/0211622 teaches a method of measuring oxidative stress by assessing samples from a subject for oxidative stress markers such as 4-hydroxyynonenal (4-HNE) from suspected AD patients versus controls (human patients) thus meeting the limitation of claims 1, 3, 5, and 6 (Figure 13; **[0008], [0009], [0011], [0059], [0138]**).

29. US 2003/0211622 teaches a method of measuring oxidative stress wherein said samples are from the hippocampus and/or cerebellum thus meeting the limitation of claims 1 and 2 (Figure 30; **[0009], [0047], [0138]**).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

30. Claims **1-6** and **10-12** are rejected under 35 U.S.C. 103(a) as being unpatentable over Schipper *et al.* (June 1995) "Expression of Heme Oxygenase-1 in the Senescent and Alzheimer-diseased Brain." Ann Neurol **37**(6): 758-768 taken with US 6,869,266 (9 February 1999) Wolozin & Coon (**IDS#AA**).

31. Schipper *et al.* teaches a method of measuring oxidative stress in Alzheimer's disease and age-matched control human patients via assessing the levels of Heme-oxygenase-1 (Abstract). Schipper *et al.* teaches measuring Heme-oxygenase-1 (HO-1) in Alzheimer's disease and age-matched control human patients thus meeting the limitations of claims 1, 4, 5, and 6 (pp. 758-759). Schipper *et al.* teaches measuring HO-1 in said patients samples from the hippocampus, cerebral cortex, and subcortical white matter thus meeting the limitations of claims 1, 2, and 3 (Figures 1-5; pp. 765). Schipper *et al.* does not teach, however, the use of olfactory neuron samples.

32. US 6,869,266 teaches a method of diagnosing Alzheimer's disease by culturing mammalian tissue containing olfactory neurons. Said tissue is isolated, cultured, and enriched to

establish an olfactory neuron culture. Said culture is then used to test for Alzheimer's disease markers (Col. 1-5; Claim 1).

33. It would be obvious to a person of ordinary skill in the art at the time the invention was made to establish an olfactory neuron culture or take an olfactory neuron culture as taught by US 6,869,266 and then measure the HO-1 in said sample to diagnose Alzheimer's disease as taught by Schipper *et al.* thus meeting the limitations of claims 3 and 10-12.

34. A person of ordinary skill in the art at the time the invention was made would have been motivated to combine the methods of Schipper *et al.* and US 6,869,266 because US 6,869,266 teaches that olfactory neurons are from the central nervous system and thus will display the pathology of any CNS disease (Col. 2-3).

35. A person of ordinary skill in the art at the time the invention was made would have a reasonable expectation of success because US 6,869,266 teaches that olfactory neurons are easily obtaining from living and dead subjects (Col. 1 & 8) and Schipper *et al.* demonstrates that HO-1 are indicative of Alzheimer's disease (Figures 4 & 5).

36. Thus the invention as a whole was *prima facia* obvious over the prior art.

37. Claims **1-6** and **10-12** are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith *et al.* (1998) "Cytochemical Demonstration of Oxidative Damage in Alzheimer Disease by Immunochemical Enhancement of the Carbonyl Reaction with 2,4-Dinitrophenylhydrazine." The Journal of Histochemistry & Cytochemistry **46**(6): 731-735 taken with US 6,869,266 (9 February 1999) Wolozin & Coon (**IDS#AA**).

38. Smith *et al.* teaches a method of measuring oxidative stress in Alzheimer's disease and age-matched control human patients via detecting 2,4-Dinitrophenylhydrazine (HNE) (Abstract). Smith *et al.* teaches measuring 2,4-Dinitrophenylhydrazine (HNE) in Alzheimer's disease and age-matched control human patients thus meeting the limitations of claims 1, 4, 5, and 6 (pp. 732; Figure 1). Smith *et al.* teaches measuring HNE in said patients samples from the hippocampus thus meeting the limitations of claims 1, 2, and 3 (Figures 1-2; pp. 732, 734). Smith *et al.* does not teach, however, the use of olfactory neuron samples.

39. US 6,869,266 teaches a method of diagnosing Alzheimer's disease by culturing mammalian tissue containing olfactory neurons. Said tissue is isolated, cultured, and enriched to establish an olfactory neuron culture. Said culture is then used to test for Alzheimer's disease markers (Col. 1-5; Claim 1).

40. It would be obvious to a person of ordinary skill in the art at the time the invention was made to establish an olfactory neuron culture or take an olfactory neuron culture as taught by US 6,869,266 and then measure the HNE in said sample to diagnose Alzheimer's disease as taught by Smith *et al.* thus meeting the limitations of claims 3 and 10-12.

41. A person of ordinary skill in the art at the time the invention was made would have been motivated to combine the methods of Smith *et al.* and US 6,869,266 because US 6,869,266 teaches that olfactory neurons are from the central nervous system and thus will display the pathology of any CNS disease (Col. 2-3).

42. A person of ordinary skill in the art at the time the invention was made would have a reasonable expectation of success because US 6,869,266 teaches that olfactory neurons are easily

obtaining from living and dead subjects (Col. 1 & 8) and Smith *et al.* demonstrates that HNE are indicative of Alzheimer's disease (Figures 1 & 2).

43. Thus the invention as a whole was *prima facia* obvious over the prior art.

44. Claims **1-6** and **10-12** are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith *et al.* (7 June 1994) "Advanced Maillard reaction end products are associated with Alzheimer disease pathology." PNAS **91**(12): 5710-5714 **(IDS#CI)** taken with US 6,869,266 (9 February 1999) Wolozin & Coon **(IDS#AA)**.

45. Smith *et al.* teaches a method of measuring oxidative stress in Alzheimer's disease and age-matched control human patients via detecting pyrraline and pentosidine (Abstract). Smith *et al.* teaches measuring pyrraline and pentosidine in Alzheimer's disease and age-matched control human patients thus meeting the limitations of claims 1, 4, 5, and 6 (pp. 5710; Figures 1 & 2). Smith *et al.* teaches measuring pyrraline and pentosidine in said patients samples from the hippocampus thus meeting the limitations of claims 1, 2, and 3 (Figure 3; pp. 5711). Smith *et al.* does not teach, however, the use of olfactory neuron samples.

46. US 6,869,266 teaches a method of diagnosing Alzheimer's disease by culturing mammalian tissue containing olfactory neurons. Said tissue is isolated, cultured, and enriched to establish an olfactory neuron culture. Said culture is then used to test for Alzheimer's disease markers (Col. 1-5; Claim 1).

47. It would be obvious to a person of ordinary skill in the art at the time the invention was made to establish an olfactory neuron culture or take an olfactory neuron culture as taught by US

6,869,266 and then measure the pyrraline and pentosidine in said sample to diagnose Alzheimer's disease as taught by Smith *et al.* thus meeting the limitations of claims 3 and 10-12.

48. A person of ordinary skill in the art at the time the invention was made would have been motivated to combine the methods of Smith *et al.* and US 6,869,266 because US 6,869,266 teaches that olfactory neurons are from the central nervous system and thus will display the pathology of any CNS disease (Col. 2-3).

49. A person of ordinary skill in the art at the time the invention was made would have a reasonable expectation of success because US 6,869,266 teaches that olfactory neurons are easily obtaining from living and dead subjects (Col. 1 & 8) and Smith *et al.* demonstrates that pyrraline and pentosidine are indicative of Alzheimer's disease (Figure 3).

50. Thus the invention as a whole was *prima facia* obvious over the prior art.

51. Claims **1-6** and **10-12** are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith *et al.* (15 April 1997) "Widespread Peroxynitrite-Mediated Damage in Alzheimer's Disease." The Journal of Neuroscience **17**(8): 2653-2657 taken with US 6,869,266 (9 February 1999) Wolozin & Coon (**IDS#AA**).

52. Smith *et al.* teaches a method of measuring oxidative stress in Alzheimer's disease and age-matched control human patients via detecting nitrotyrosine (NT) (Abstract). Smith *et al.* teaches measuring nitrotyrosine (NT) in Alzheimer's disease and age-matched control human patients thus meeting the limitations of claims 1, 4, and 5 (pp. 2653). Smith *et al.* teaches measuring NT in said patients samples from the hippocampus thus meeting the limitations of

claims 1, 2, and 3 (Figures 1-2; pp. 2653, 2656). Smith *et al.* does not teach, however, the use of olfactory neuron samples.

53. US 6,869,266 teaches a method of diagnosing Alzheimer's disease by culturing mammalian tissue containing olfactory neurons. Said tissue is isolated, cultured, and enriched to establish an olfactory neuron culture. Said culture is then used to test for Alzheimer's disease markers (Col. 1-5; Claim 1).

54. It would be obvious to a person of ordinary skill in the art at the time the invention was made to establish an olfactory neuron culture or take an olfactory neuron culture as taught by US 6,869,266 and then measure the NT in said sample to diagnose Alzheimer's disease as taught by Smith *et al.* thus meeting the limitations of claims 3 and 10-12.

55. A person of ordinary skill in the art at the time the invention was made would have been motivated to combine the methods of Smith *et al.* and US 6,869,266 because US 6,869,266 teaches that olfactory neurons are from the central nervous system and thus will display the pathology of any CNS disease (Col. 2-3).

56. A person of ordinary skill in the art at the time the invention was made would have a reasonable expectation of success because US 6,869,266 teaches that olfactory neurons are easily obtaining from living and dead subjects (Col. 1 & 8) and Smith *et al.* demonstrates that NT are indicative of Alzheimer's disease (Figures 1-2).

57. Thus the invention as a whole was *prima facia* obvious over the prior art.

58. Claims **1-6** and **10-12** are rejected under 35 U.S.C. 103(a) as being unpatentable over Nunomura *et al.* (15 March 1999) "RNA Oxidation Is A Prominent Feature of Vulnerable

Neurons in Alzheimer's Disease." The Journal of Neuroscience **19**(6): 1959-1964 (**IDS#CC**) taken with US 6,869,266 (9 February 1999) Wolozin & Coon (**IDS#AA**).

59. Nunomura *et al.* teaches a method of measuring oxidative stress in Alzheimer's disease and age-matched control human patients via detecting 8-hydroxyguanosine (8OHG) (Abstract). Nunomura *et al.* teaches measuring 8-hydroxyguanosine (8OHG) in Alzheimer's disease and age-matched control human patients thus meeting the limitations of claims 1, 4, and 5 (pp. 1959-1961; Figure 2). Nunomura *et al.* teaches measuring 8OHG in said patients samples from the hippocampus, subiculum, as well as the entrohinal, frontal, temporal, and occiptal neocortex thus meeting the limitations of claims 1, 2, and 3 (Figure 1; pp. 1959-1961). Nunomura *et al.* does not teach, however, the use of olfactory neuron samples.

60. US 6,869,266 teaches a method of diagnosing Alzheimer's disease by culturing mammalian tissue containing olfactory neurons. Said tissue is isolated, cultured, and enriched to establish an olfactory neuron culture. Said culture is then used to test for Alzheimer's disease markers thus meeting the limitations of claims (Col. 1-5; Claim 1).

61. It would be obvious to a person of ordinary skill in the art at the time the invention was made to establish an olfactory neuron culture or take an olfactory neuron culture as taught by US 6,869,266 and then measure the 8OHG in said sample to diagnose Alzheimer's disease as taught by Nunomura *et al.* thus meeting the limitations of claims 3 and 10-12.

62. A person of ordinary skill in the art at the time the invention was made would have been motivated to combine the methods of Nunomura *et al.* and US 6,869,266 because US 6,869,266 teaches that olfactory neurons are from the central nervous system and thus will display the pathology of any CNS disease (Col. 2-3).

63. A person of ordinary skill in the art at the time the invention was made would have a reasonable expectation of success because US 6,869,266 teaches that olfactory neurons are easily obtaining from living and dead subjects (Col. 1 & 8) and Nunomura *et al.* demonstrates that 8OHG are indicative of Alzheimer's disease (Figure 1).

64. Thus the invention as a whole was *prima facia* obvious over the prior art.

65. Claims **1-6** and **10-12** are rejected under 35 U.S.C. 103(a) as being unpatentable over Horie *et al.* (18 July 1997) "Immunohistochemical Localization of Advanced Glycation End Products, Pentosidine, and Carboxymethyllysine in Lipofusin Pigments of Alzheimer's Disease and Aged Neurons." Biochemical and Biophysical Research Communications **236**(2): 327-332 taken with US 6,869,266 (9 February 1999) Wolozin & Coon (**IDS#AA**).

66. Horie *et al.* teaches a method of measuring oxidative stress in Alzheimer's disease and age-matched control human patients via detecting pentosidine and carboxymethyllysine (Abstract). Horie *et al.* teaches measuring pentosidine and carboxymethyllysine (CML) in Alzheimer's disease and age-matched control human patients thus meeting the limitations of claims 1, 4, 5, and 6 (pp. 336-337). Horie *et al.* teaches measuring pentosidine and CML in said patients samples from the hippocampus thus meeting the limitations of claims 1, 2, and 3 (Figures 1-3).

67. US 6,869,266 teaches a method of diagnosing Alzheimer's disease by culturing mammalian tissue containing olfactory neurons. Said tissue is isolated, cultured, and enriched to establish an olfactory neuron culture. Said culture is then used to test for Alzheimer's disease markers thus meeting the limitations of claims (Col. 1-5; Claim 1).

68. It would be obvious to a person of ordinary skill in the art at the time the invention was made to establish an olfactory neuron culture or take an olfactory neuron culture as taught by US 6,869,266 and then measure the CML in said sample to diagnose Alzheimer's disease as taught by Horie *et al.* thus meeting the limitations of claims 3 and 10-12.

69. A person of ordinary skill in the art at the time the invention was made would have been motivated to combine the methods of Horie *et al.* and US 6,869,266 because US 6,869,266 teaches that olfactory neurons are from the central nervous system and thus will display the pathology of any CNS disease (Col. 2-3).

70. A person of ordinary skill in the art at the time the invention was made would have a reasonable expectation of success because US 6,869,266 teaches that olfactory neurons are easily obtaining from living and dead subjects (Col. 1 & 8) and Horie *et al.* demonstrates that CML are indicative of Alzheimer's disease (Figure 3).

71. Thus the invention as a whole was *prima facia* obvious over the prior art.

Summary

72. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is **(571) 272-0889**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Brenda Brumback** can be reached on **(571) 272-0961**.

The fax number for the organization where this application or proceeding is assigned is **703-872-9306**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see **http://pair-direct.uspto.gov**. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

Elizabeth C. Kemmerer

CJN
July 27, 2004

ELIZABETH KEMMERER
PRIMARY EXAMINER